No. 2022-1461

In the United States Court of Appeals
For the Federal Circuit

BAXALTA INCORPORATED, BAXALTA GMBH,
Plaintiffs - Appellants

v.

GENENTECH, INC.,
Defendant - Appellee

Appeal from the United States District Court for the District of Delaware
No. 1:17-cv-00509, Hon. Timothy B. Dyk

REPLY BRIEF OF APPELLANTS

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ARGUMENT IN REPLY

Baxalta's opening brief demonstrated that a reasonable jury could find the claims enabled. Taking the facts and drawing all inferences in Baxalta's favor, the hybridoma-and-screening process detailed in the specification allows a skilled artisan to generate new embodiments—monoclonal antibodies that bind Factor IX/IXa and increase the procoagulant activity of Factor IXa ("exhibit procoagulant activity")—without undue experimentation. And after generating the claimed antibodies, skilled artisans could apply well-known antibody engineering techniques to engineer them into any claimed isotype or format.

Genentech's primary argument is that the hybridoma-and-screening process constitutes undue experimentation as a matter of law because it involves screening. *See, e.g.*, Genentech Br. 41 (arguing that "[m]ake-and-screen strategies . . . have been repeatedly held to require undue experimentation"). But this argument cannot be correct: the hybridoma-and-screening process at issue is materially indistinguishable from the process that this Court held was enabled in *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). This Court cannot affirm on this basis without overruling *Wands*.

When it retreats from overbroad arguments about "make-and-screen," Genentech's brief underscores the disputes of material fact that render summary judgment inappropriate, including:

- whether the hybridoma-and-screening process is "iterative," requiring "trial-and-error" akin to hunting for a needle in a haystack or is a reliable, predictable process yielding new claimed antibodies every time it has been followed, *compare* Genentech Br. 3-4, 25, 30-32, 36-37, 41, 43, *with* Baxalta Br. 4, 28, 44, 49-52;

- whether the disclosed fusion experiment number 195 generated claimed antibodies, *compare* Genentech Br. 11, 39, *with* Baxalta Br. 9, 23-24, 40-41, 46;

- whether, after obtaining antibodies having the claimed functionality by following the patent's disclosure, skilled artisans could make predictable changes to obtain the claimed isotypes and formats of those antibodies, *compare* Genentech Br. 34-37, *with* Baxalta Br. 11-18, 32-37;

- whether skilled artisans could humanize claimed antibodies without undue experimentation, *compare* Genentech Br. 12-13, 34-35, 52, *with* Baxalta Br. 14-15, 34-35; and

- whether skilled artisans could use any specificity (or only certain specificities) for the second binding arm when engineering a bispecific antibody with one arm that binds Factor IX/IXa and increases procoagulant activity, *compare* Genentech Br. 53-54, 57-58, *with* Baxalta Br. 35-37.

At the summary judgment stage, for each of these factual questions, Genentech bore the burden to prove that a reasonable jury would necessarily decide the issue in its favor by clear and convincing evidence. Genentech carried that burden for none.

Summary judgment was improper. The judgment below should be reversed and the case remanded.

I. A Reasonable Jury Could Find Facts Under Which the '590 Patent Satisfies the Enablement Requirement.

In addressing the *Wands* factors, Genentech erroneously blends together the two steps (involving materially different technologies) to practice the full scope of

the claims: (1) employing a hybridoma-and-screening process to generate new antibodies that bind Factor IX/IXa and exhibit procoagulant activity; and (2) using antibody engineering techniques to make predictable changes to these antibodies (in the regions not responsible for binding) to change their isotype and format while preserving their binding specificity and procoagulant activity.

This Court's precedent makes clear that "the predictability of the art" is a key factor in enablement. *McRO, Inc. v. Bandi Namco Games Am. Inc.*, 959 F.3d 1091, 1102 (Fed. Cir. 2020); *see also* Baxalta Br. 31. When arts are predictable, "a single embodiment" can enable a broad claim. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987).

This principle is critical. A patent need not disclose, for example, working examples of IgD antibodies when skilled artisans know that the constant regions of a claimed IgG antibody can be replaced with IgD constant regions to create a claimed IgD antibody that binds Factor IX/IXa and exhibits procoagulant activity.

Like the district court, Genentech's analysis blurs together the two steps of practicing the full scope of the claims. The correct analysis, demonstrated in Baxalta's opening brief, shows that neither (1) producing claimed antibodies from a hybridoma-and-screening process; nor (2) engineering these antibodies into the claimed isotypes and formats involves undue experimentation.

A. A Reasonable Jury Could Find that Using a Hybridoma-and-Screening Process to Generate Antibodies that Bind Factor IX/IXa and Exhibit Procoagulant Activity Does Not Require Undue Experimentation.

The '590 Patent enables skilled artisans to make new embodiments—new antibodies that bind Factor IX/IXa and exhibit procoagulant activity—through a hybridoma-and-screening process that is materially indistinguishable from the hybridoma-and-screening process held enabled in *Wands*. As in *Wands* (and unlike *Idenix* and *Wyeth*), screening is used only to identify **which** antibodies practice the claims, not **whether** any antibodies practice the claims.

1. Taking the facts in the light most favorable to Baxalta, the hybridoma-and-screening process taught in Example 1 and Example 2 succeeded every time it was followed.

The inventors conducted four hybridoma fusion experiments. Appx145 at 10:11-13. It is undisputed that three experiments produced claimed antibodies: the inventors either disclosed the amino acid sequences of or deposited antibodies produced by experiments 193, 196, and 198. Genentech disputes only whether a fourth experiment, number 195, succeeded. Genentech Br. 11, 39.

The specification indicates that it did, reciting that master clones producing a FIX/FIXa binding antibody and exhibiting procoagulant activity were selected and subcloned from "each fusion experiment":

> From each fusion experiment, several (5-15) master clones (selected from the master plate) were identified and subjected to subcloning. After 3 rounds of sub-cloning, most of the cell lines were

> homogenous as demonstrated by ELISA and chromogenic activity analysis (see FIG. 4) as well as by cDNA sequence analysis. A specific master clone and all its subclones produce the same FIX/FIXa binding antibody.

Appx146 at 12:14-22. The master clones (and subclones) were selected because of their procoagulant activity ("FVIII-like activity"). Appx146 at 11:11-17, 11:51-54.

On its face, "each fusion experiment" includes fusion experiment 195, and nothing in the specification indicates that experiment 195 was an exception to the subcloning process. A reasonable jury could infer that following subcloning, "each fusion experiment," including number 195, produced isolated antibodies that bound Factor IX/IXa and exhibited procoagulant activity. *See* Appx20571.

Genentech notes that the wells on the master plate included pools of different hybridoma cell clones, inferring that when the inventors said they selected "master clones" from the master plates, they truly selected "wells." Genentech Br. 9-10, 28-29, 39. Genentech then questions whether a well exhibiting procoagulant activity necessarily means that one clone within the well would exhibit the activity when isolated. *Id*. But even if selecting "master clones" could be read as selecting "wells," nothing in the specification—or anywhere else in the record—suggests that a pool of antibodies might exhibit procoagulant activity even if no isolated antibody within that pool would exhibit procoagulant activity. And Genentech's argument ignores the specification's statements that a routine and well-known subcloning process was

followed for each fusion experiment. Appx146 at 12:14-17, 11:16-18. This is, at most, a factual dispute.

Drawing the inferences in Baxalta's favor, fusion experiment 195 succeeded. At a minimum, even if fusion experiment 195's result is treated as unknown, the hybridoma-and-screening process of Example 1 and Example 2 produced new antibodies every time for which the results are known. *See Wands*, 858 F.2d at 739-40 (rejecting the treatment of unknown results as failures). Genentech did not show (much less by clear and convincing evidence) that the hybridoma-and-screening process has failed to produce claimed antibodies. *See* Genentech Br. 39 (arguing only that there is no evidence of success for fusion experiment 195).

2. The predictable, hybridoma-and-screening process does not involve "trial-and-error."

The testimony of Baxalta's expert confirms the specification: "[I]f you follow the conventional methods set forth in the patent, . . . you **will** find a subpopulation [of antibodies] that do, in fact, increase the procoagulant activity of Factor IXa[.]" Appx16449 (emphasis added); Appx16451 ("[I]t takes the unknown out of whether or not you're going to get them[.]").

Rather than address this evidence, Genentech relies on repeated mischaracterizations of the process as "trial and error," searching for a needle in a haystack. *E.g.*, Genentech Br. 31-32. But repetition does not create truth.

Baxalta addressed this point fully in its opening brief (at 3, 4, 28, 44, 49-52). There is no "trial and error;" no guesswork. When the process is followed, antibodies that bind Factor IX/IXa and exhibit procoagulant effect are produced. Screening identifies which antibodies practice the claims rather than whether any antibodies practice the claims.

That fact distinguishes this case from *Idenix Pharm. LLC v. Gilead Sciences Inc.*, 941 F.3d 1149 (Fed. Cir. 2019), and *Wyeth & Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380 (Fed. Cir. 2013), in which no process reliably (much less consistently) generated new embodiments without undue experimentation.

Like the district court, Genentech's argument rests on a logical flaw: Because there is a small number of a claimed antibodies among a large number of candidates, producing them must be as difficult as finding a needle in a haystack. Genentech Br. 43. And if synthesizing and identifying new embodiments was difficult in *Idenix* and *Wyeth*, then (Genentech reasons) it must be equally difficult here. Genentech Br. 32, 43-44.

But these arguments beg the question, assuming away the key point. In the light most favorable to Baxalta, the record shows, unlike in *Idenix* and *Wyeth*, that the claimed antibodies can be reliably obtained through a disclosed process that requires only routine experimentation. What matters is that the process yields antibodies having the claimed functionality, not the number of antibodies produced.

Genentech argues, in effect, that make-and-screen processes can never, as a matter of law, be enabling. No case supports such a sweeping proposition, and as detailed below, this Court held the make-and-screen process of *Wands* to be enabling. Whether a make-and-screen process enables the claims depends on the specific facts of the claims and technology at issue. Broad generalizations are no substitute for the case-specific analysis mandated by this Court. *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1088 (Fed. Cir. 2021).

Facts matter, and Genentech's assertions about trial-and-error, iterative processes, and needles in haystacks cannot substitute for evidence. A reasonable jury could find that the process for obtaining new claimed antibodies does not involve undue experimentation.

3. Genentech cannot distinguish *Wands*, which held that a materially identical process was enabled.

The district court's conclusion that this reliable hybridoma-and-screening process involved undue experimentation cannot be harmonized with *Wands*, which held that a materially indistinguishable process was enabled. Baxalta Br. 41-43.

Genentech's discussion of *Wands* is inconsistent with its broader argument that any claim requiring screening must, as a matter of law, involve undue experimentation. As noted, Genentech repeatedly (and incorrectly) characterizes the process for practicing the '590 Patent as "trial and error," merely searching for a needle in a haystack. Genentech Br. 3-4, 25, 36-37, 41, 43.

But Genentech's characterizations would apply equally to *Wands*' hybridoma-and-screening process.[1] If Genentech's principal argument—that screening equates to non-enablement as a matter of law—were correct, then *Wands* was wrongly decided, and thirty-six years of settled caselaw should be overturned.

When addressing *Wands*, Genentech changes course, abandoning its generalizations about trial-and-error and conceding that claims involving making and screening antibodies can be enabled. Now what matters (according to Genentech) is not the need for screening but the screening's yield rate: According to Genentech, the 44% yield rate of *Wands* enables claims, but a lower yield rate does not. This argument rests on nothing more than bare assertion. Genentech never identifies any source of a "yield" requirement in this Court's enablement jurisprudence. Nor does it offer any explanation for why, when following the same screening step, finding more equates to enablement and finding fewer equates to non-enablement. Genentech Br. 40.

Genentech's argument conflicts with this Court's analysis in *Wands*, which did not focus on the number of hybridomas that were successfully screened but on the success of "the entire attempt to make a monoclonal antibody against a particular antigen":

[1] And they would apply equally to *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367 (Fed. Cir. 1986), which also held a hybridoma-and-screening process enabled.

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibod[ies] with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. . . . [I]n the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. . . . Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations.

858 F.2d at 740. Like Wands, the inventors of the '590 Patent were successful in making at least one claimed antibody each time they conducted their experiment.[2]

What mattered to this Court's analysis in *Wands* was that the hybridoma-and-screening experiment did not require undue experimentation, not the specific yield rate of the screening step. Like practicing the claims at issue, Wands screened only to determine **which** antibodies practiced the claims, not **whether** antibodies practiced the claims. As in *Wands*, Genentech presents no evidence that following the hybridoma-and-screening process of Examples 1 and 2 involves undue experimentation.

Moreover, in relying on the "44%" yield rate, Genentech misreads *Wands*. Genentech focuses on the nine hybridomas analyzed by Wands, noting that "four produced antibodies that fell within the claims." *Id.* at 739. Genentech then

[2] Or, at a minimum, for the three fusion experiments for which the results are known.

compares this success rate against the screening process in the '590 Patent for Factor VIII-like activity. Genentech Br. 40.

But Genentech overlooks that these nine hybridomas passed through earlier screening steps. Wands first screened the hybridoma cells to determine whether they bound HBsAg. *See* 858 F.2d at 738 ("[B]y screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest. Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg."). And from the hybridoma cells that produced antibodies directed against HBsAg, Wands then conducted a second screening, discarding hybridomas that bound less than 10,000 cpm (a measurement of binding strength). *See id.* ("Antibodies that bound at least 10,000 cpm in the commercial radioimmunoassay were classified as 'high binders.' Using this criterion, 143 high-binding hybridomas were obtained."). The nine hybridomas discussed by Genentech were among the 143 high binders that passed the second screen.

Genentech is thus wrong when it asserts that 44% of the hybridomas produced by Wands (or even 44% of the hybridomas that secreted antibodies against HBsAg) practiced the claimed invention. Genentech's comparison of the 1.6% statistic from the inventors of the '590 Patent to 44% from *Wands* is one of apples and oranges.

This analysis (and Genentech's confusion) confirms the error in Genentech's approach to enablement. Enablement does not turn on the yield rate of particular screening steps but whether the hybridoma-and-screening experiment to develop an antibody with desired characteristics, as a whole, involves undue experimentation. *Id.* at 740. As in *Wands*, the hybridoma-and-screening step here does not involve undue experimentation and has been successful every time.

4. The *Wands* factors confirm that, as in *Wands*, the make-and-screen process disclosed in the specification enables the claimed invention.

a. The specification provides significant guidance, and minimal experimentation is necessary.

The specification guides skilled artisans to make antibodies having the claimed functional characteristics with minimal experimentation. The specification provides substantial guidance about using a chromogenic assay to detect Factor IXa-activating antibodies, leaving skilled artisans in a better position than the inventors to practice the invention. Baxalta Br. 44-45.

Genentech suggests that this argument was forfeited. Genentech Br. 33-34. Not so. In discussing this *Wands* factor, Baxalta previously emphasized that "the specification's guidance on modifying a commercially-available chromogenic assay is so detailed 'that the POSITA need not experiment to determine any necessary modifications in the first instance.'" Appx18865; *see also* Appx18863-18867

(discussing the guidance about the screening protocol); Appx18844 (noting "detailed instructions" for "quickly screening").

Genentech also notes that "the Asserted Claims do not require any particular assay." Genentech Br. 33.[3] But enablement merely requires that the "specification . . . enable any person skilled in the art . . . to make and use the [invention]." 35 U.S.C. § 112. This Court has never held that the specification's guidance is relevant only when it is the only way to practice the claims. *See Wands*, 858 F.2d at 737.

Nor does Genentech address the specification's detailed guidance about the necessary modifications to the chromogenic assay. As the inventor testified, these modifications solved the "fundamental technical problem" that made identification of these antibodies possible. Appx16866.

Genentech accuses Baxalta of arguing that its claims "should be subject to some lower enablement standard." Genentech Br. 33. In truth, Baxalta notes (correctly) the fact that the specification's guidance "pave[s] the way" for skilled artisans is highly relevant to the *Wands* factor of "the amount of direction or guidance presented." 858 F.2d at 737.

[3] Genentech's reference to previously rejected claim construction arguments is irrelevant to this appeal. Genentech Br. 33-34. Neither party has asked this Court to reverse the district court's claim construction in this appeal, and Baxalta relies on that construction on appeal.

Crediting Baxalta's evidence, which must occur at this stage, the level of guidance is significant. And the quantity of experimentation is low: It would not require "substantial time and effort" to make and use the claimed invention. Appx19197-19198.

b. The specification provides significant working examples.

In discussing working examples, Genentech complains that Baxalta is violating the parties' stipulation, Genentech Br. 27-29, but its argument misreads the stipulation and conflates two different concepts.

There are eleven Disclosed Antibodies for which the amino acid sequences—the complete structures—are known. Baxalta Br. 10, 46-47; Appx20571-20572 at ¶ 14 & n.1. Baxalta never stipulated that these were the only antibodies that practiced the claims; it stipulated that these were the only antibodies sequenced or deposited. *See* Appx20569-20572.

But the specification indicates that the inventors identified 30 to 50 antibodies that bound Factor IX/IXa and exhibited procoagulant effect. Baxalta Br. 46.[4] Baxalta noted this in its summary judgment opposition: "Although not included in Dr. Marasco's structural diversity analysis because no amino acid sequence is

[4] Genentech identifies that Figure 1 of the patent includes a typographical mistake regarding labeling of the assay. In its opening brief, Baxalta noted Figure 1 only in its Statement of the Case (Baxalta Br. 9-10) and did not mention or rely on it at all in the argument on this issue (*see* Baxalta Br. 46-47 (not mentioning Figure 1)).

provided, the ’590 Patent describes additional isolated antibodies that fall within the claims.” Appx18854 at 12 n.3; Appx16438-16439. Indeed, if “1.6% of the antibodies [the inventors] tested ended up increasing procoagulant activity,” Genentech Br. 38, then they would have identified 15 antibodies per fusion experiment. *See* Appx146 at 11:25 (noting the testing of “ten 96 well plates”).

This Court’s analysis in *Wands* indicates that all discovered antibodies—not merely those with known amino acid sequences—are relevant to enablement. The opinion recites that Wands deposited a “single hybridoma,” but this Court treated all of his successes as relevant, not merely the single antibody with known amino acid sequences. 858 F.2d at 736. As in *Wands*, the inventors’ full successes matter, not merely the Disclosed Antibodies with known amino acid sequences.

Genentech also makes the puzzling assertion that Baxalta forfeited the argument that the Disclosed Antibodies reflect the structural diversity of the claimed genus. Genentech Br. 51-52. Baxalta briefed this at length in its summary judgment opposition. *See* Appx18846-18850. More importantly, Genentech has the burden of proof, and Genentech makes no attempt to show that any antibodies within the claimed genus are meaningfully distinct in structure from the Disclosed Antibodies.

c. The breadth of the claims is small and narrow.

Genentech does not deny that the claims cover only a focused and small genus of antibodies (Baxalta Br. 47-48) but argues that this fact weighs against enablement:

"The fewer procoagulant antibodies that exist among all of the antibodies that bind Factor IX, the harder it is for a skilled artisan to find them without undue experimentation." Genentech Br. 25.[5]

Genentech's assertion lacks evidentiary support. The record shows that these antibodies—despite their small number—are easy to find without undue experimentation by following the process described in Examples 1 and 2 of the specification. Baxalta Br. 40-47. Genentech's unsupported attorney argument is no substitute for evidence.

d. The state of the prior art is advanced; relative skill of those in the art is high; and the process is predictable.

Genentech acknowledges that the skill in the art is "high" and that skilled artisans are familiar with the hybridoma-and-screening process. Genentech Br. 29-30.

Genentech notes that "the '590 Patent does not teach a skilled artisan how to know **in advance** which antibodies" bind Factor IX/IXa or increase the procoagulant activity. Genentech Br. 30 (emphasis added). Genentech misses the point: the specification teaches a process that predictably produces antibodies having the claimed functionality. The relevant question is not whether patentees "know in

[5] Genentech treats breadth of the claims as a Catch-22. If claims are broad, their broad scope weighs against enablement because more must be enabled. And if claims are narrow, their narrow scope weighs against enablement because (Genentech assumes) the embodiments are harder to identify.

advance" which antibodies will practice the claims but whether the process used to practice the claims requires undue experimentation. Here, the process disclosed in the specification reliably and without undue experimentation produces claimed antibodies.

* * *

Genentech's assertion that hybridoma-and-screening processes constitute undue experimentation as a matter of law cannot be harmonized with *Wands*. On the record of this case, viewing the facts and drawing all inferences in favor of Baxalta, a reasonable jury could find that using the hybridoma-and-screen process to produce claimed antibodies does not require undue experimentation.

B. A Reasonable Jury Could Find that Engineering Antibodies into the Claimed Isotypes and Formats Is a Predictable Art That Does Not Require Undue Experimentation.

A jury could also find that once in possession of claimed antibodies, skilled artisans could make "predictable changes . . . to arrive at other types of antibodies" that also exhibit the claimed functionality without undue experimentation. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) (describing the standard for predictable arts in the context of antibodies).

1. After obtaining antibodies having the claimed functionality, engineering a claimed antibody from one isotype or format to another is a predictable art.

The specification makes the predictability clear, noting that well-known engineering techniques can be used to change a claimed antibody's isotype or format. A "class switch" (between isotypes of claimed antibodies) may be "caused in a directed manner by means of genetic engineering methods ('directed class switch recombination'), as is known from the prior art." Appx143 at 6:41-44. A claimed humanized antibody can be created by inserting "complement[arity] determining regions (CDRs) from murine monoclonal antibodies" into "the framework regions of selected human antibody sequences." Appx143 at 6:49-52. "Fab fragments" or "$F(ab)_2$ fragments" can be "derived from monoclonal antibodies." Appx143 at 6:30-33.

This type of antibody engineering—modifying a claimed antibody's constant regions to arrive at a claimed antibody with a different isotype or format—epitomizes a predictable art. Baxalta Br. at 31-37. Genentech cannot credibly dispute these teachings, particularly under the summary judgment standard. It never denies that skilled artisans can—and do—perform similar antibody engineering and achieve the predicted results. Nor does it squarely assert that this aspect of the art is unpredictable.

The most Genentech can do is echo the district court's conclusion that success is not absolutely guaranteed and that skilled artisans perform confirmatory tests. Genentech Br. 35. But Genentech's standard has no grounding in this Court's precedent. Predictable arts do not require absolute certainty of success. *See Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371-72 (Fed. Cir. 2011) (characterizing adapting "the safety mechanisms of the prior art cigarette lighters . . . to fit a utility lighter" as a predictable art, "even if it required some variation in the selection or arrangement of particular components"). Testing is hardly unknown to the mechanical arts, and it is likewise not unknown here.

Nor does routine confirmatory testing defeat enablement. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive."); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) (in discussing expectation of success, holding that that experiments "to verify the [predicted] physicochemical characteristics of each salt" are merely routine experimentation). As in *Pfizer*, "one skilled in the art would have had a reasonable expectation of success" in making the claimed invention and "merely had to verify that expectation" using routine experimentation. 480 F.3d at 1367. Routine confirmatory testing does not transform a predictable art into an unpredictable one.

2. Genentech ignores the testimony of Baxalta's expert regarding humanization that, at minimum, creates a triable issue of fact.

The only specific antibody engineering technique discussed by Genentech is humanization, for which it quotes the same testimony as the district court. Genentech Br. 35, 52. But this testimony suggests, at most, that humanization might involve more experimentation than other forms of antibody engineering. *Id*. It does not show that every reasonable jury must find (by clear and convincing evidence) that humanization involves **undue** experimentation, particularly in light of the contrary evidence. Baxalta Br. 34-35.

And even if a humanized antibody "does not have the same effectiveness as the original," Genentech Br. 35 (quoting Appx16432), the antibody would still be within the scope of the claims, which do not require any particular efficacy.

Like the district court, Genentech ignores the testimony of Baxalta's expert that by performing "modifications within known parameters," a skilled artisan could "get [humanization] to work precisely." Appx16432 (Dr. Marasco). Baxalta highlighted this evidence. Baxalta Br. 34-35. Genentech's silence confirms that it has no answer. At minimum, this testimony creates a triable issue of fact.

3. Genentech's arguments about bispecific antibodies are misplaced.

Genentech similarly fails to respond to Baxalta's arguments regarding bispecific antibodies. Genentech argues non-enablement on the ground that the '590

Patent does not teach any particular specificity for the second binding arm. Genentech Br. 53-54. But as Baxalta explained, this argument erroneously assumes that skilled artisans need to be taught the specificity of the second binding arm to make bispecific antibodies. Baxalta Br. 34-37.

This point goes unanswered. Genentech never identifies evidence that bispecific antibodies binding Factor IX/IXa and increasing procoagulant activity work only with particular binding specificities of the second binding arm (and thus that skilled artisans would need to be instructed which second arms can and cannot be used). Indeed, record evidence indicates the opposite. Appx144 at 7:2-36; Appx19776; Appx16838. Taking the facts in Baxalta's favor, a skilled artisan could choose **any** binding specificity for the second arm.

An ordinary monospecific antibody is like a key ring with two identical keys. Making a claimed antibody bispecific is like replacing one key with a different key. The first key still works, no matter what second key is used.

Similarly, a skilled artisan in possession of a binding arm of a claimed antibody (i.e., an antibody that binds Factor IX/IXa and exhibits procoagulant activity) would know that the binding arm could be used in an antibody with two copies of that binding arm (a monospecific antibody) or could be used in an antibody with one copy of that binding arm and one copy of another (a bispecific antibody). Appx19776; Appx16838. Whether it has one or two copies of the Factor IX/IXa

arm, the antibody still exhibits the claimed functionality. No further teaching was necessary to enable skilled artisans to make and use the invention in the form of a bispecific antibody.

If there were any doubt, the specification confirms the knowledge of the art, directing skilled artisans to *Bispecific Antibodies as Novel Bioconjugates* (1998), Appx144 at 7:2-36, which discloses a variety of techniques for making bispecific antibodies. And Genentech's own expert admitted that the pre-1999 literature taught skilled artisans how to make them. Appx19776. As named inventor Dr. Scheiflinger made clear, the reason the specification did not contain detailed instructions for making bispecific antibodies was not because **so little** was known about them but rather because **so much** was known about them: "Bispecifics have been known for a long time, why would we put anything here in this patent[?]" Appx16838.

Taking the evidence in the light most favorable to Baxalta, the '590 Patent enables skilled artisans to make and use bispecific antibodies in which one arm binds Factor IX/IXa and increases procoagulant activity. Genentech identifies no evidence that skilled artisans needed further teaching about the second arm to practice a claimed bispecific antibody. Genentech's theory that enablement required the inventors to teach a particular specificity for the second binding arm thus has no support in the record or in this Court's precedent. *See, e.g.*, *DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985) ("Not every last detail is to be described, else

patent specifications would turn into production specifications, which they were never intended to be.") (quoting *In re Gay*, 309 F.2d 769, 774 (CCPA 1962)).

4. Genentech's reliance on *Amgen* is misplaced.

Genentech does not defend the district court's erroneous comparison of the binding sites in *Amgen Inc. v. Sanofi*, 987 F.3d 1080 (Fed. Cir. 2021), to the claimed isotypes and formats or its assertion that working examples were required. *See* Baxalta Br. 37-40. Genentech nonetheless relies heavily on *Amgen*, Genentech Br. 3-4, 36-37, 41-43, 50-51, but its arguments conflict with the decision's reasoning.

The *Amgen* claims required binding to specific residues, 987 F.3d at 1083, a requirement that defined the "functional breadth" of the claims. *Id.* at 1083 & n.1; *see also id.* at 1083 ("The claimed antibodies are defined by their function: binding to a combinations of sites (residues) on the PCSK9 protein, in a range from one residue to all of them; and blocking the PCSK9/LDLR interaction.").

Because the claims' functional breadth required binding specific residues, the *Amgen* patent needed to enable antibodies binding each of the claimed residues. But it did not. The *Amgen* patent did not teach any means of generating antibodies that bound to specific claimed residues. Nor did the *Amgen* patent provide examples of antibodies binding to all of the claimed residues:

> [T]here are three claimed residues to which not one disclosed example binds. And although the claims include antibodies that bind up to sixteen residues, none of Amgen's examples binds more than nine.

Id. at 1087 n.1 (internal citations omitted). "[T]he disclosed species and guidance only abide[d] in a corner of the [claimed] genus." *Id.* at 1087 (internal quotation marks omitted).

For example, a skilled artisan seeking to practice the claims with an antibody that bound to "C375"—a function specifically claimed in *Amgen*—would have no way to do so. Indeed, it is unclear whether such an antibody even exists and could be produced with *any* amount of experimentation.

Genentech misreads *Amgen* by asserting that Amgen's patents disclosed "working examples of antibodies that bound those specific residues." Genentech Br. 42. This is wrong—the heart of this Court's enablement analysis was that Amgen "claimed residues to which not one disclosed example binds." 987 F.3d at 1087 n.1.

Genentech continues its misreading, stating that Amgen "determined where on PCSK9 an antibody should bind" and "which parts of PCSK9 other such antibodies should bind to." Genentech Br. 42. Again, this assertion was true only for some claimed combinations of binding residues. For other combinations of binding residues specifically claimed by Amgen, whether antibodies that bind to these combinations even exist is speculative, 987 F.3d at 1087 & n.1, and even if they exist, producing them would have indisputably required undue experimentation.

In Genentech's view, *Amgen*'s requirement that the antibody bind to specific residues was irrelevant to enablement (and, if anything, made enablement more likely). Genentech Br. 42. But this argument directly conflicts with this Court's analysis, which rested on the claims' failure to enable functions that they expressly claimed, binding to the specific claimed combinations of residues: "The binding limitation is itself enough here to require undue experimentation." 987 F.3d at 1087; *see also Soitec, S.A. v. Silicon Genesis Corp.*, 81 F. App'x 734, 738 (Fed. Cir. 2003) (holding that when a patent expressly claims "A or B," the specification "must fully enable" both "A" and "B"). This Court held that having specifically claimed antibodies with the function of binding to specific residues (e.g., "C375") and specific combinations of residues (e.g., all sixteen), enablement required Amgen to enable these antibodies. It did not.

Genentech commits the error warned against in *Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 93 F.3d 1572 (Fed. Cir. 1996), which reversed a district court (in the written description context) for "confus[ing] a claim not supported by the specification, which is not allowable, with a broad claim, which is." *Id.* at 1582 n.7; *see also id.* ("If Fox did not consider the precise location of the lockout to be an element of his invention, he was free to draft claim 24 broadly (within the limits imposed by the prior art) to exclude the lockout's exact location as a limitation of the claimed invention.").

Genentech's *Amgen* arguments conflict with this Court's reasoning and rest on a principle for which there is no support.

* * *

Practicing the full scope of the claims at issue requires two steps: (1) obtaining antibodies that bind Factor IX/IXa and exhibit procoagulant activity through a hybridoma-and-screening process; and (2) engineering those antibodies into any claimed isotype or format. Under this Court's precedent and the record, at minimum, a genuine issue of material fact exists as to whether either step requires undue experimentation. A reasonable jury could conclude that the claims are enabled, and this Court can reverse and end its analysis here.

II. Genentech Cannot Defend the District Court's Additional Errors.

The discussion above shows that under the *Wands* factors and this Court's test for enablement, a reasonable jury could find the claims enabled. The district court erred by imposing additional requirements.

A. Genentech's request to extend *MagSil* is meritless.

As Baxalta explained, the district court's extension of *MagSil Corp. v. Hitachi Global Storage Technologies, Inc.*, 687 F.3d 1377, 1379 (Fed. Cir. 2012), is unprecedented. Baxalta Br. 55-57. *MagSil* involved claims that recited a specific range of measurement. The quality (resistive changes) was already known, and the quantitative measurement distinguished the prior art. Here, the claimed functionality

was entirely unknown in the prior art. Unlike in *MagSil*, the invention was not a matter of degree when measured against the prior art but rather the existence of the claimed functionality (binding and procoagulant activity) itself.

No case has applied *MagSil* to claims without a quantitative range improvement. Genentech does not dispute this point. It has no response to (and does not acknowledge) the cases that have refused this extension. Baxalta Br. 56-57. For example, the reasoning of *ABS Global, Inc. v. Inguran, LLC,* No. 14-cv-503-WMC, 2019 WL 4276647 (W.D. Wis. Sept. 10, 2019), is thoughtful and persuasive, but Genentech does not answer it.

Nor does Genentech reconcile the untenable consequences that follow from this extension of *MagSil*. No patent reciting a function could survive this enablement test unless it claimed a specific and narrow measurement. Baxalta showed (at 55 n.17) the irrationality of the district court's reasoning when applied to the patent in *FastShip, LLC v. United States*, 892 F.3d 1298 (Fed. Cir. 2018). Again, having no answer, Genentech ignores the argument.

This Court's holding in *CFMT, Inc. v. Yieldup International Corp.*, 349 F.3d 1333 (Fed. Cir. 2003), is on point. Baxalta Br. 57-58. Because the patent claimed an "improvement" without claiming a specified numerical range, "the disclosure enable[d] that invention by showing improvements in the overall system." 349 F.3d at 1338.

Genentech attempts to distinguish *CFMT* as involving method claims. Genentech Br. 49-50. But *CFMT* did not turn on the claims reciting a method rather than a composition. Instead, because the patent did not "clai[m] a system that achieved cleanliness up to a specified numerical particle-free range," enablement did not "require disclosure of a method that enables one of ordinary skill to achieve that [hypothetical] range without undue experimentation." 349 F.3d at 1338. Genentech cannot distinguish *CFMT*.

B. Genentech cannot defend the district court's requirement that Baxalta enable antibodies outside the claims.

The district court's opinion criticizes Baxalta for asserting that "a compound is not within the scope of the claims if the procoagulant effect is only caused by a bispecific antibody's arm that binds to Factor X." Appx75.

Far from being a "convoluted argument" "offered for the first time at the Summary Judgment hearing," this truth follows from the claim construction, which requires binding Factor IX/IXa to play a role in increasing procoagulant activity. Baxalta Br. 58-59.

Genentech cannot defend this error. It agrees (as it must) that a bispecific antibody "is not within the scope of the claims if the procoagulant effect is only caused by a bispecific antibody's arm that binds to Factor X." Appx75; *see* Genentech Br. 49.

Instead, Genentech attempts to rewrite the district court's opinion. But the opinion speaks for itself, and the error is apparent: bispecific antibodies are within the claims only if the Factor IX/IXa arm exhibits procoagulant activity, and Baxalta was not required to enable unclaimed antibodies.

C. The district court erred in considering the accused product.

Genentech cannot defend the district court's erroneous focus on the accused product or its requirement that the patent "enable the accused antibody, emicizumab." Appx73.

Instead, Genentech accuses Baxalta of interjecting a "best mode" issue into the district court's opinion. Genentech Br. 55-56. Genentech misses the point. As Baxalta explained, the district court's reasoning **resembles** a heightened best mode requirement: The district court apparently reasoned that because emicizumab (a humanized bispecific antibody binding Factor X and Factor IXa) is the best form of the claimed antibody, enablement required the inventors to identify and teach this form. Baxalta Br. 59-60. But the enablement inquiry is whether a skilled artisan, without undue experimentation, could make a bispecific antibody binding Factor IXa and exhibiting procoagulant activity. The district court erred by requiring the inventors to identify and disclose the (supposed) optimal binding specificity for the second arm.

1. The time required to develop emicizumab does not disprove enablement.

Genentech reprises the district court's reliance on the time it took Chugai to develop emicizumab. Genentech Br. 55. But as Baxalta explained, this post-priority evidence is irrelevant because there is no evidence that Chugai followed the process taught by the '590 Patent. *See* Baxalta Br. 61-62; *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360-61 & n.29 (Fed. Cir. 1998) (rejecting post-priority evidence because the expert "did not copy the protocol described" in the specification). Genentech notably does not assert that Chugai followed the '590 Patent's teachings.

2. Even if the relative effectiveness of emicizumab were relevant, the district court erred in weighing the evidence.

Enablement does not require Baxalta to enable a particular measurement of procoagulant activity.

But if it matters, the experts dispute how to measure antibodies' procoagulant activity. Baxalta Br. 62-63. Genentech claims that Baxalta's argument was forfeited, Genentech Br. 58, but the district court made its comparison of assays *sua sponte*, relying on a comparison not pressed by either party. *See* Appx51; Appx68-69; Appx73-74 & n.20 (noting and apparently rejecting the opinion of Baxalta's expert). Baxalta had no opportunity to respond to the comparison, and under regional circuit law, an argument is preserved when it is "passed upon" (*i.e.*,

addressed) by the district court. *See Sprauve v. W. Indian Co. Ltd.*, 760 F. App'x 101, 103 n.3 (3d Cir. 2019).

On the merits, Genentech cannot defend the district court. Dr. Krishnaswamy explained that Genentech's experts erroneously analyzed emicizumab's antibody activity without accounting for concentration. Appx19519-195120; Appx19524-19525. The district court apparently misunderstood this testimony, treated the measurements as absolute antibody activity, and then compared measurements between assays to find that emicizumab's activity "far exceeds" that of the Disclosed Antibodies. Appx74 & n.20; *see also* Appx51; Appx68-69.

Far from defending the district court, Genentech now argues that these measurements are "noncomparable" because "198/A1 was assessed using a chromogenic assay . . . while emicizumab was assessed using a thrombin-generation assay." Genentech Br. 59 (citing Appx116, Appx6606). This argument proves Baxalta's point: these assays are the source of the "10%" and "3.75%" activity figures relied on by the district court. Appx19519-195120; Appx19524-19525.

If comparing the results of these assays were proper, then the district court erred by failing to account for the concentration levels. But if "no reasonable jury could credit" a comparison between the assays, Genentech Br. 59, then the district court erred by comparing them. Either way, the district court erred.

At a minimum, Genentech's arguments confirm that it has not shown that every reasonable jury must find by clear and convincing evidence that emicizumab's procoagulant activity exceeds that of the Disclosed Antibodies.

CONCLUSION

Enablement requires only that a skilled artisan be able to make and use the full scope of the claimed invention without undue experimentation. Taking the evidence and drawing all inferences in the light most favorable to Baxalta, the full scope of the claims is enabled through a two-step process:

(1) Using a hybridoma-and-screening process (materially indistinguishable from that in *Wands*) that reliably produces new antibodies having the claimed functionality, i.e., that bind Factor IX/IXa and exhibit procoagulant activity; and

(2) Applying well-known antibody engineering techniques to those antibodies to make the full scope of claimed isotypes and formats.

Neither step involves undue experimentation. The judgment below should be reversed and the case remanded.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

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